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| BAUSCH, SARAE L | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/055,728 | VAN DER KUYL ET AL. | |
| | Examiner | Art Unit | |
| | Sarae Bausch | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-5,7,9,10,12-19,21 and 24-41* is/are pending in the application.

4a) Of the above claim(s) *7,13,25-28,35-37 and 39-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,9,10,12,14-19,21,24,29-34 and 38* is/are rejected.

7)☒ Claim(s) *38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Status*

1. Currently, claims 1, 3-5, 7, 9-10, 12-19, 21, and 24-41 are pending in the instant application. Claims 2, 6, 8, 11, 20, and 22-23 are cancelled. Claims 7, 13, 25-28, 35-37, and 39-41 have been withdrawn from consideration as being drawn to a nonelected invention. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented, as necessitated by amendment, or are reiterated from the previous office action. They represent the complete being presently applied to the instantly examined claims. Response to arguments follow. This action is Non-Final.

### *Withdrawn Rejections*

2. The rejections of claims 1, 12, 19, 33, and 38, under 35 U.S.C. 112, second paragraph, made in section 5, page 3-4 of the previous office action, is withdrawn in view of the amendment to the claims.

3. The rejections of claims 1-3, 9-10, 19 and 29, under 35 U.S.C. 102(b), made in section 9, page 13-14 of the previous office action, is withdrawn in view of the amendment to the claims.

4. The rejections of claims 1-3, 9-11, and 19, under 35 U.S.C. 102(b), made in section 10, page 14-15 of the previous office action, is withdrawn in view of the amendment to the claims.

5. The rejections of claims 1-3, 6, 9-11, 19, and 21-22 under 35 U.S.C. 102(b), made in section 11, page 15 of the previous office action, is withdrawn in view of the amendment to the claims.

6. The rejections of claims 1-3, 6, 9-11, 19, 21-22, 24, 29-30 under 35 U.S.C. 102(b), made in section 12, page 15-16 of the previous office action, is withdrawn in view of the amendment to the claims.

7. The rejections of claims 1, 4-5, 9-10, and 19, under 35 U.S.C. 102(b), made in section 13, page 16-17 of the previous office action, is withdrawn in view of the amendment to the claims.

8. The rejections of claims 1-6, 9-10, 19, 21-22, 24, and 29-30, under 35 U.S.C. 101, made in section 15, page 17-18 of the previous office action, is withdrawn in view of amendment to the claims.

## *Claim Objections*

9. Claim 38 is objected to because of the following informalities: claim 38 recites a method of providing a kit comprising nucleic acids comprising SEQ ID No. 72 and 81 and/or proteinaceous molecules capable of specifically bind to SialoAdhesin or TIE 1. Since applicant has received an action on the merits for the originally presented invention, method of detecting an expression product by hybridization of a nucleic acid (see office action, 11/01/2004), this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 38 is objected to because it contains subject matter that was not elected by original presentation and will be examines to the extent it applies to the elected subject matter. Applicant is requested to withdrawn the non-elected subject matter from the claim. See 37 CFR 1.142(b) and MPEP § 821.03.

10. Appropriate correction is required.

## *New Grounds of Rejection*

***Claim Rejections - 35 USC § 112***

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 19, 33, 34 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a). Claim 19 and 38 recite a method for determining whether an individual possesses a Kaposi's sarcoma tumor cell. However the final process step is one of using the levels of expression to determine the presence or absence of a tumor cell. The final process step is not within the scope of the preamble; the final process step determines the presence of any tumor cell while the preamble sets forth a method for determining a Kaposi's sarcoma tumor cell. Accordingly, it is indefinite as to whether the claim is intended to be limited to methods of determining a Kaposi's sarcoma tumor cell as referred to in the preamble or a method of determining any tumor cell. Applicant should amend the claim to indicate how if the claims are for a method of determining a Kaposi's sarcoma tumor cell or any tumor cell.

(b). Claim 33 recites a method for determining the presence of a Kaposi's sarcoma tumor cell. However the final process step is using the level of expression to determine the presence or absence of a tumor in an individual. The recitation of "a tumor", which encompasses multiple tumor cells, in the final process step is not within the scope of the preamble. The final process steps determines the presence of any tumor, while the preamble sets forth a method for determining a Kaposi's sarcoma tumor cell. Accordingly, it is indefinite as to whether the claim is intended to encompass methods of determining the presence or absence of any tumor or

limited to determining the presence of a Kaposi's sarcoma tumor cell as referred to in the preamble. Applicant should amend the claim to indicate if the claims are for a method of determining a Kaposi's sarcoma tumor cell or any tumor.

(c). Claim 34 recites a method for diagnosing presence of disease comprising comparing expression of isolated sequence of SEQ ID No. 72 and 81 or parts or analogues thereof in an individual to a reference value. However, the final process step is comparing the expression of isolated sequences to reference values. The final process step determines expression of isolated sequences, while the preamble sets forth a method of diagnosing presence of disease. Accordingly, it is indefinite as to whether the claim is intended to be encompass method of diagnosing presence of disease or limited to comparing the expression of an isolated sequence to a reference value. Applicant should amend the claim to indicate if the claims are for a method of diagnosing presence of disease or determining expression of isolated sequences to reference values.

***Claim Rejections - 35 USC § 112 – Written Description***

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 19 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 19 is drawn to a method for determining whether an individual possesses a Kaposi's sarcoma tumor cell and/or site of angiogenesis comprising determining whether a sample comprises expression products of Sialoadhesin and Tie 1. While the specification asserts that a nucleotide sequence of sialoadhesin is SEQ ID No. 72 depicted in figure 8 and TIE 1 sequence as SEQ ID No. 81 depicted in figure 17 (see page 7, paragraph 0020), it does not however teach or describe the entire gene that is associated with this acronym. Further, the specification asserts that the sequences are identified by name and GenBank number in figures 2-18 and other identification can be found in tables 1-4. However, none of the figures or tables list the GenBank numbers associated with SEQ ID No. 72 and 81. GenBank accession number, NM_023068 reports teach the gene Sialoadhesin has an alternative splice variant that is soluble rather than membrane-bound (see page 2). The claims are broadly drawn to any gene with the acronym of Sialoadhesin or Tie-1 and encompass any Sialoadhesin or Tie-1 gene from any source. The art teaches that the acronym, sialoadhesin is used to abbreviate a family of different genes from different sources. Mucklow et al. (Genomics, 1995, 28:344-346) teach that sialoadhesin acronym refers to a family of genes, which includes CD22, myelin-associated glycogenprotein (MAG), CD 33, and sialoadhesin (see pg. 344, 1st column, 1st full paragraph). The specification provides no teaching or description of any of these sialoadhesin proteins or Tie-1 protein, let alone an association of these sialoadhesin proteins or Tie-1 protein with Kaposi's sarcoma tumor cell. The art teaches sialoadhesin represents an entire family of genes in addition to specific genes with variants, and the specification does not describe which

sialoadhesin gene or protein or which Tie-1 gene or protein is used to determine whether an individual possesses a Kaposi's sarcoma tumor cell and/or site of angiogenesis. Based on the lack of written description in the specification, the skilled artisan would not know which sequences fall within the large genus of the sialoadhesin and Tie-1 expression encompassed by the recitation of the claims.

Claim 34 is drawn to a method of diagnosing presence of disease comprising comparing expression of isolated sequences of SEQ ID No. 72 and 81 or parts or analogues thereof. The recitation of "parts and analogues" encompasses many variants of SEQ ID No. 72 and 81 and the specification does not teach or provide working examples illustrating which parts or analogues of SEQ ID No. 72 and 81 would be functionally active to diagnose the presence of any disease. Thus, the scope of the claims includes numerous functional variants of SEQ ID No. 72 and 81 (diagnosis of presence of disease) and the genus is highly variant because a significant number of differences between genus members is permitted. The specification and claim does not provide any guidance as to what part or analogues of SEQ ID No. 72 or 81 would diagnose any disease. Functional activity assays that could distinguish the parts or analogues of SEQ ID No. 72 and 81 that diagnose the presence of any disease are missing from the specification. Furthermore, the claims read on "a part" of SEQ ID No. 72 or 81 that broadly encompasses as few as two nucleotides of SEQ ID No. 72 or 81 from any source. The specification does not describe any functional assay that would allow one of skill in the art to determine if as few as two nucleotides in length from any source would be predictably correlative of diagnosing any disease.

*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed sialoadhesin, Tie-1 genes, nor the parts or analogues of SEQ ID No. 72 and 81 regardless of the complexity or simplicity of the method of diagnosing a disease or determining whether an individual possesses a Kaposi's sarcoma tumor cell and/or site of angiogenesis. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993), and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In *Fiddes v. Baird*, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the

> invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

***Claim Rejections - 35 USC § 112- Enablement***

15. Claims 1,3-5, 9, 10, 12, 14-19, 21, 24, 29-34 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are broadly drawn to a method of determining efficacy of treatment by a change in the status of Kaposi's sarcoma tumor cells by obtaining a sample after initiating treatment and determining whether sample comprises a change in level of an expression product of SEQ ID No. 72 and 81. The methods are further drawn to samples comprising blood samples and peripheral blood mononuclear cells obtained within one week and two days of initiating

treatment, and expression of SEQ ID No. 72 and 81 is quantified and comprises genes involved in generation, maintenance, and/or breakdown of blood vessels. The claims are also drawn to a method of detecting an expression product of SEQ ID No. 72 and 81 comprising obtaining a sample, introducing a nucleic acid into the sample, and determining whether the nucleic acid hybridizes to the sample and are further drawn to a tumor cell, comprising Kaposi's Sarcoma, and a site of angiogenesis. Claims are also drawn to a method of determining whether an individual possesses a site of angiogenesis by determining whether a hemopoetic cell from individual comprise an altered amount of expression product of SEQ ID No. 72 and 81 as compared to a reference value, and further drawn to a hemopoietic cell comprising a peripheral blood mononuclear cell. The claims are also drawn to a method of determining the presence of Kaposi's sarcoma cell in an individual by obtaining a sample from the individual and detecting the level of peripheral blood mononuclear expression of SEQ ID No 72 and 81. The claims are also drawn to a method of determining the presence of a Kaposi's sarcoma tumor cell by obtaining a sample from an individual and detecting the level of peripheral blood mononuclear cell expression of SEQ ID No 72 and 81 and by providing a diagnostic kit, obtaining a sample, and quantifying an expression product of SEQ ID No. 72 and 81. The claims are drawn to diagnosing the presence of any disease comprising comparing expression of isolated SEQ ID No. 72 and 81 or parts or analogues thereof in an individual to a reference value.

Guidance in the Specification

The specification asserts a change in expression product of a marker gene is indicative for whether a treatment is effective or not by the level of expression, which can be enhanced or reduced. The specification asserts the expression product of the marker gene is preferably

quantified and the level of expression product of marker genes can vary from patient to patient (see paragraph 10, page 4). The specification further asserts that a very sensitive expression detection system will typically detect expression product where a less sensitive system detects no expression product and a person of skill in the art is well capable of designing the most appropriate expression detection system to practice this preferred embodiment (see paragraph 10, page 5), however the specification does not teach the most appropriate expression detection system to detect expression of SEQ ID No. 72 and 81. The specification asserts that in a preferred embodiment the tumor comprises Kaposi's sarcoma. The specification asserts that Kapposi's sarcoma is a disease of proliferating blood vessels and is very much suited for identifying marker genes, preferably SEQ ID No. 72 and 81, involved in angiogenesis (see paragraph 12, page 5). The specification asserts further that angiogenic mechanism causing the lesions of Kaposi's Sarcoma is an interplay of viral and cellular gene expression and is poorly understood in terms of which genes are involved and what controls their expression (see paragraph 13, page 6). Further, the angiogenic proliferation of Kaposi's sarcoma is likely to be universal in angiogenesis and marker genes for angiogenesis are very suitable for determination of whether a treatment of Kaposi's sarcoma is effective (see paragraph 13, page 6).

The specification asserts a method of determining gene expression patterns in Kaposi's Samoa by serial analysis of gene expression (see paragraph 18, page 6). The specification asserts that the use of a nucleic acid comprising a sequence of Seq ID No 72 and 81 can be used as a detection marker for the process of angiogenesis in the course of regenerative treatment and changes in expression level of the detection marker indicate active growth of blood vessels (see paragraph 23, page 9). However, the specification does not teach how much change in

expression level of SEQ ID No. 72 or 81 indicates active growth of blood vessels. The specification further asserts that it is possible to monitor a specific status of an individual, the presence of a disease, or developing the disease (see paragraph 26, page 10). However, the specification further states the absence of a marker gene in a sample can be indicative for the presence of a disease or for danger of developing the disease (see paragraph 26, page 10) and that a decreasing amount of expression product in samples in a specific time period can indicate – either beneficial or harmful – process. The specification does not give any guidance on how to determine if the presence or absence of the marker genes, SEQ ID No. 72 and 81, is indicative of disease, developing disease, or not having the disease at all or how to determine if the expression amount is beneficial or harmful.

Working Examples

The specification teaches obtaining SAGE libraries of two patients with Kaposi's Sarcoma that were not treated and obtaining SAGE libraries of one patient after 24 hours of chemotherapy treatments and after 48 hours of treatment and determining the expression profiles of the samples (see page 14-16, examples 1-3).. The specification teaches determining markers in skin samples of 5 different samples with Kaposi Sarcoma and 2 control samples without Kaposi's Sarcoma (see example 10, page 33 and figure 19). The specification teaches determining gene expression levels of sequences in peripheral blood mononuclear cell sample by taking blood samples of 4 different patients with Kaposi's Sarcoma and two different patients without Kaposi's Sarcoma and analyzing expression levels (see example 11, page 41 and figure 20). However, the specification provides no indication as to whether the results were statistically

significant such that the skilled artisan would be able to predictably correlate the results with the presence of a tumor cell, diagnosis of disease, or efficacy of treatment of disease.

The following are unclear from the teachings in the specification. The specification envisions hypothetical situations where SEQ ID No. 72 and 81 could determine the presence of a Kaposi's sarcoma tumor cell, angiogensis, disease and efficacy of any treatment of a Kaposi's sarcoma tumor cell associated with Kaposi's sarcoma. The specification appears to be conceiving of possible scenarios where the expression level could be either enhanced or decreased and that these results would indicate the presence – or absence – of a Kaposi's sarcoma tumor cell however, it is unclear how one of skill in the art would determine the level of expression necessary to determine the presence of the Kaposi's sarcoma tumor cell or angiogenesis. Furthermore, the specification does not teach how to diagnose any disease by comparing the expression of SEQ ID No. 72 and 81 or part or analogue, thereof. For example, the specification does not teach which part or analogue of SEQ ID No. 72 and 81 would diagnose any disease. Specifically, the specification does not teach how to determine how much of a change in expression in Seq ID No 72 or 81 would indicate the presence of Kaposi's sarcoma tumor cell or angiogenesis. Further, it is unclear if a change in expression of Seq ID No 72 and 81 would even indicate the presence of a Kaposi's sarcoma tumor cell or how this change would relate to the efficacy of treatment of a Kaposi's sarcoma tumor cell. The specification does not teach how to detect SEQ ID No. 72 and 81 that is indicative of angiogensis nor does it teach how to determine if the expression amount of the marker gene which is beneficial or harmful. Further, it is unclear how to determine if the altered amount of expression is indicative of the presence of a non-hemopoietic cell. The specification lacks guidance on how SEQ ID No. 72

and 81, found in the study on Kaposi's sarcoma, are suitable for determining if any treatment is effective and further it is unclear how SEQ ID No. 72 and 81 relate to angiogenesis. It is unclear how one of skill in the art would design the most appropriate expression detection system to practice this preferred embodiment and assess the efficacy of the results of the embodiments.

The unpredictability of the art and the state of the prior art

There is a large body of knowledge in the prior art related to angiogenesis in general, and their association with tumor identification, as well as drug or therapeutic response. However, the art is highly unpredictable with regard to the angiogenic status of an individual or the routine assessment of the effect of a given treatment on tumor angiogenesis. Post filing art, Ruegg et al. teaches that to date there is no validated laboratory test to determine the angiogenic status of an individual patient and to routinely assess the effect of a given treatment on tumor angiogenesis (Current Molecular Medicine 2003, 3, pp. 673-691, see specifically page 685, 2nd column, 1st paragraph). It is unpredictable whether any such marker would be associated with angiogenesis and accurately determine a disease state, a physiological state, or drug metabolism or response. For example, Ruegg et al. teaches that developing a test is an enormous challenge with far reaching clinical implications and many reputable academic and pharmaceutical research laboratories are currently engaged in such effort. Ruegg et al. teach that developing a marker specific to a tumor vasculature would require identification of a new marker, from four different samples: the angiogenic endothelial cell, the plasma from same patient, endothelial cells from corresponding healthy tissues from same patients and/or healthy donors, and plasma from healthy individuals (see page 685, 2nd column, 2nd paragraph and figure 4). Even in a case where an association between a particular transcription profiles and an angiogenic disorder,

Kaposi's Sarcoma (KS), was found to exist, such as with the applicant's own work ( van der Kuyl et al., BMC Cancer 2002 2(1):21) of comparing a patient with AIDS-KS and the effectiveness of treatment by determining a mRNA profile after 24 and 48 hours after therapy to two untreated patients, van der Kuyl et al. found that based on genetic expression profiles the libraries of the treated patient after 48 hours were more closely related to patients untreated than the treated patient after 24 hours (see page 7, 2nd column 1st paragraph), suggesting that the association between transcription profiles, angiogenic disorder, and treatment prognosis is unpredictable. Further, applicant's own post filing art (Cornelissen et al, BMC Cancer 2003 3:7), teaches a study of semi-quantative PCR analysis of six genes profiles that were found to have increased expression in KS tissue samples and found only one of the six gene expressions had a $P<0.05$ compared to normal skin tissue (see page 9, 1st column, 1st full paragraph and figure 3). Further, figure 3 shows that the other five gene expression profiles of the KS tissue samples are within error of the normal skin tissue samples (see Figure 3, page 12). Cornelissen et al. specifically teaches that it is unpredictable to determine based on gene expression of KS samples an association between angiogenic disorder, diagnosis, and treatment efficacy since Cornelissen et al. shows that normal tissue samples are within error of KS tissue samples. Additionally, van der Kuyl et al. shows a difference in gene expression profiles after 24 and 48 hours after treatment of the same patient, which indicates the unpredictability of determining if a treatment will be effective based on gene expression.

In the instant case, the specification appears to envision scenarios where SEQ ID No. 72 and 81 and parts and analogues expression levels could be used to indicate the presence – or absence – of a Kaposi sarcoma tumor cell, angiogenesis, or any disease. It is unclear how one of

skill in the art would determine the level of expression or what part or analogues of SEQ ID No. 72 and 81 would be necessary to determine the presence of the Kaposi sarcoma tumor cell, efficacy of treatment, angiogensis, or diagnosis of any disease considering the unpredictably of the art. The prior art, along with applicant's own post filing art, supports the unpredictability of this area of technology.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to the determining the amount of change in expression of SEQ ID No. 72 and 81, or part or analogue of SEQ ID No. 72 and 81, to determine the presence of a Kaposi's sarcoma tumor cell and a non-hemopoeitic cell, efficacy of treatment, and relation of the marker genes to angiogenesis in any individual or diagnosis of any disease, and along with the evidence in the art with regard to the variance of determining treatment efficacy by gene expression specifically for angiogenesis, the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study in different populations to determine if in fact there was either an association between SEQ ID No. 72 and 81, and which parts or analogues of SEQ ID No. 72 and 81 would be present in individuals with Kaposi's Sarcoma or any other angiogenic disease relative to individuals without any angiogenic disease. The results of such a study are completely unpredictable as evidence by the evidence presented in applicant's own post filing date art (which reflects the current state of the art) with regard to the gene expression profile of a Kaposi's Sarcoma patient to comparison of normal gene expression profile without the disorder

and the variance in expression levels after treatment. Further, post filing art Ruegg et al. teach developing a test to determine the angiogenic status of an individual is an enormous challenge (see Figure 4). The claims are broadly drawn to method of determining efficacy of treatment in a Kaposi's sarcoma tumor cell, determining whether an individual possesses angiogenesis and diagnosing the presence of any disease. To practice the invention as broadly as it is claimed, the skilled artisan would have to determine that SEQ ID No. 72 and 81 would be specific for the Kaposi's sarcoma tumor cell and determine how much expression would be associated with Kaposi's sarcoma tumor cell to determine if the individual would posses the Kaposi's sarcoma tumor cell. Further, the skilled artisan would have to determine the change in expression values to assess the efficacy of treatment on the Kaposi sarcoma tumor cell. Such experiments are unpredictable, as evidence by the post filing date art and require extensive experimentation and a large research study with a large sample size. The skilled artisan would have to screen each gene profile expression to determine those that possess a Kaposi sarcoma tumor cell in all populations. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression profiles would predictably determine a susceptibility or diagnosis to a Kaposi sarcoma tumor cell or angiogenesis. The skilled artisan would have to perform undue experimentation to determine which part or analogue of SEQ ID No. 72 and 81 would be predictably correlated to diagnosis of any disease. Given the lack of guidance in the specification and the conflicting evidence in the art, such analysis is replete with unpredictable experimentation and is considered undue.

***Response to Arguments***

16. The response traverses the rejection on page 11-15 of the response mailed 7/11/2005. The response asserts on page 11, subsection A, that one of skill in the art could select and design the most appropriate system for detecting expression products of SEQ ID Nos. 72 and 81 because the specification teaches that a person of skill in the art is well capable of designing the most appropriate expression system to practice this embodiment and that one of high skill would be capable of determining which expression detection system would be more appropriate than others based on expression product, expression levels, cost, and availability of reagents. This response has been thoroughly reviewed but not found persuasive because even if one of high skill in the art would be able to determine an expression system to determine the detection of a marker gene, one of high skill in the art would not be able to determine which expression system would be most appropriate to determine the detection of Kaposi's sarcoma tumor cell, treatment efficacy of Kaposi's sarcoma tumor cell, angiogenesis, and diagnosis of any gene using SEQ ID No. 72 or 81 because the specification does not enable one of high skill in the art to diagnosis any disease, determine the efficacy of any treatment in Kaposi's sarcoma tumor cell, or angiogenesis using the marker genes, SEQ ID No. 72 and 81 and any expression detection, regardless of the ability to determine the most appropriate expression detection system.

The response asserts on page 12, section B, that the specification does teach how much change in the expression level of a detection marker may indicate active growth of blood vessels. The response asserts that the specification, paragraph 23, provides that a nucleic acid comprising a sequence depicted in Figures 1-18 and table 1 or table 2 can be used as detection marker for the process of angiogenesis and table 1 provides an "overexpression factor" with as little as 2 to as

great as 30 fold to indicate the active growth of blood vessels, which supports that any change in the expression level of the detection marker may indicate the active growth of blood vessels. This response has been thoroughly reviewed but not found persuasive. Neither table 1 or 2 teach SEQ ID No. 72 or 81 as a detection marker for the process of angiogensis. Paragraph 23 is merely prophetic, stating that SEQ ID No. 72 or 81 or a part or analogue thereof can be used as an indicator for angiogenesis but the specification does not provide a working example or a detection expression level to determine angiogenesis using the markers SEQ ID No. 72 and 81. The specification appears to be conceiving of possible scenarios where the expression level could be enhanced and that these results would indicate the presence – or absence – of a angiogensis however, it is unclear how one of skill in the art would determine the level of expression necessary to determine angiogenesis using SEQ ID No. 72 and 81.

The response further asserts on page 12 cont'd to page 13, section B, that the amended claims are directed to Sialoadhesin and TIE1 and parts or analogues of these two genes and assert that the specification, paragraph 12, states that Kaposi's sarcoma is a disease of proliferating blood vessels and as shown in figure 19, SEQ ID No. 72 increases expression in Kaposi's sarcoma and therefore increased levels of SEQ ID No. 72 expression products indicate a growth of blood vessels. The response asserts that figure 20 depicts increase level of expression of SEQ ID No. 81 in Kaposi's sarcoma patient which indicate a growth in blood vessels. This response has been thoroughly reviewed but not found persuasive. As stated in the previous office action, it is highly unpredictable to determine the angiogenic status of an individual or the routine assessment of the effect of a given treatment on tumor angiogenesis. Post filing art, Ruegg et al. teaches that to date there is no validated laboratory test to determine

the angiogenic status of an individual patient and to routinely assess the effect of a given treatment on tumor angiogenesis (Current Molecular Medicine 2003, 3, pp. 673-691, see specifically page 685, 2nd column, 1st paragraph). It is unpredictable whether any such marker would be associated with angiogenesis and accurately determine a disease state, a physiological state, or drug metabolism or response. For example, Ruegg et al. teaches that developing a test is an enormous challenge with far reaching clinical implications and many reputable academic and pharmaceutical research laboratories are currently engaged in such effort. Ruegg et al. teach that developing a marker specific to a tumor vasculature would require identification of a new marker, from four different samples: the angiogenic endothelial cell, the plasma from same patient, endothelial cells from corresponding healthy tissues from same patients and/or healthy donors, and plasma from healthy individuals (see page 685, 2nd column, 2nd paragraph and figure 4). Even in a case where an association between a particular transcription profiles and an angiogenic disorder, Kaposi's Sarcoma (KS), was found to exist, such as with the applicant's own work (van der Kuyl et al., BMC Cancer 2002 2(1):21) of comparing a patient with AIDS-KS and the effectiveness of treatment by determining a mRNA profile after 24 and 48 hours after therapy to two untreated patients, van der Kuyl et al. found that based on genetic expression profiles the libraries of the treated patient after 48 hours were more closely related to patients untreated than the treated patient after 24 hours (see page 7, 2nd column 1st paragraph), suggesting that the association between transcription profiles, angiogenic disorder, and treatment prognosis is unpredictable. Furthermore, the specification asserts that angiogenic mechanism causing the lesions of Kaposi's sarcoma is an interplay of viral and cellular gene expression and is poorly understood in terms of which genes are involved and what controls their expression

(see paragraph 13, page 6). The specification further states that the angiogenic proliferation of Kaposi's sarcoma is likely to be universal in angiogenesis and marker genes for angiogenesis are very suitable for determination of whether a treatment of Kaposi's sarcoma is effective (see paragraph 13, page 6).

The response asserts on page 13, section C, that the claims as amended are not directed to the absence of a marker gene being indicative of a disease, developing a disease, or not having a disease at all and the claims, as amended, are not directed to determining if an expression amount is beneficial or harmful. This response has been thoroughly reviewed but not found persuasive. Claim 33, as amended, is broadly drawn to a determining the presence or absence of a tumor in an individual by detecting levels of expression, which broadly encompasses detecting the presence or absence of a specific marker gene. Claim 19 is broadly drawn to a method of determining whether an individual possesses Kaposi's sarcoma tumor cell by determining if the sample comprises expression products Sialoadhesin or TIE 1 which broadly encompasses determining the presence or absence of a marker gene. Claim 34 is broadly drawn to a method of diagnosing any disease by comparing expression of isolated sequences of SEQ ID No. 72 and 81 or parts or analogues thereof to a reference value, which broadly encompasses the presence or absence of a marker gene. Furthermore, the specification asserts that it is possible to monitor a specific status of an individual, the presence of a disease, or developing the disease (see paragraph 26, page 10) (instant claim 34) and further states the absence of a marker gene in a sample can be indicative for the presence of a disease or for danger of developing the disease (see paragraph 26, page 10) and that a decreasing amount of expression product in samples in a specific time period can indicate – either beneficial or harmful – process. The specification does

not give any guidance on how to determine if the absence of the marker genes, SEQ ID No. 72 and 81, is indicative of disease, developing disease, or not having the disease at all, as required by claim 34.

The response asserts on page 13, section D, that the application does not claim the use of an altered amount of expression to determine the presence of a non-hemopoietic cell and as such applicant is not required to enable such a determination. Remarks with regard to non-hemopoietic cells have withdrawn from the rejection due to the amendments to claim 21.

The response asserts on page 14, section E, that applicants are not required to guarantee 100% success of the methods in the course of enabling others to practice the invention. The response asserts that figures 19 and 20 have error bars which do no overlap, suggesting that these results are statistically significant and can be predictably correlated with the results. The response further asserts that persons using the method outlined in the specification were enabled to gain consistent results and refer to Cornellissen et al (BMC cancer 2002, 2, 21). Applicants assert that the specification provides statistically significant changes and that the specification enables the practice of the invention showing statistically significant changes. This response has been thoroughly reviewed but not found persuasive. Figures 19 and 20 do not provide statistically significant data to predictably correlate an expression of SEQ ID No. 72 and 81 with angiogensis or diagnosing any disorder. Neither figure 19 or 20 clearly demonstrate that the error bars do not overlap. If applicant is going to rely on figure 19 and 20 for providing statistically significant data, applicant needs to supply a higher resolution copy of figures 19 and 20 than originally filed. The resolution of Figure 19 and 20, as originally filed, is very limited and it is not clear that the error bars do not overlap. Furthermore, applicant is relying upon Cornellissen et

al., BMC Cancer 2002, vol. 2, pg. 21 for providing statistically relevant data in figure 3. It is noted that Cornellissen et al, BMC Cancer 2002, vol. 2, p. 21 does not contain any statically significant results with the data presented and figure 3 is the effect of chemotherapy in cycling cells, which is not found persuasive. If applicant meant for Cornellissen et al, BMC Cancer 2003, vol. 3, pp. 1-15 to provide support for statistically significant data, it is noted that this figure 3, teaches a study of semi-quantitative PCR analysis of six genes profiles that were found to have increased expression in KS tissue samples and found only one (Tie-1) of the six gene expressions had a $P<0.05$ compared to normal skin tissue (see page 9, 1st column, 1st full paragraph and figure 3). Figure 3 shows that the other five gene expression profiles of the KS tissue samples are within error of the normal skin tissue samples (see Figure 3, page 12). Cornelius et al. specifically teaches that it is unpredictable to determine based on gene expression of KS samples an association between angiogenic disorder, diagnosis, and treatment efficacy since Cornelius et al. shows that normal tissue samples are within error of KS tissue samples and provides only statistically significant results for only one of six genes, which further demonstrated the unpredictability to correlate expression with KS samples and angiogenic disorder, diagnosis, and treatment efficacy.

The response asserts on page 15, section F, that the specification does teach how much change in expression in SEQ ID No. 81 indicates the present of a target cell in Kaposi's sarcoma. Applicant refers to SEQ ID No. 30 as being indicative of SEQ ID No. 81 and table 2 shoes an increase expression of 2-10 fold in Kaposi's sarcoma. Applicant also refers to van der Kuyl et al. (BMC cancer 2002, 2, 21) which shows that levels of TIMP fall to normal levels upon treatment (table 5). This response has been thoroughly reviewed but not found persuasive. The

specification does not teach an expression factor for SEQ ID No. 81. Only claim 34 is drawn to a part or analogue thereof of SEQ ID No. 81 and therefore the specification provides no example of treatment efficacy and expression level of SEQ ID No. 81. With regard to van der Kuyl et al. and the assertion that the level of TIMP fall to normal levels upon treatment which enables one of high skill in the art to determine if a treatment is effective using a marker gene, the claims are not drawn to a determining if treatment is effective in using the marker gene, TIMP; the claims are drawn to a method of determining treatment efficacy using SEQ ID No. 72 and 81. Furthermore, van der Kuyl et al. found that based on genetic expression profiles the libraries of the treated patient after 48 hours were more closely related to patients untreated than the treated patient after 24 hours (see page 7, 2nd column 1st paragraph), suggesting that the association between transcription profiles, angiogenic disorder, and treatment prognosis is unpredictable.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

***Double Patenting***

17. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 1, 3-5, 9, 12, 14-19, 21, 24, 31-34, and 38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12, 14-28, and 30-33 of copending Application No. 10/310677. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1-12, 14-28, and 30-33 of application 10/310677 is generic and coextensive in scope to all that is recited in instant claims 1, 3-5, 9, 12, 14-19, 21, 24, 31-34, and 38 of the pending application. That is instant claim 1, 12, 19, 21, 32, 33, 34 and 38 falls entirely in the scope of claim 7-8, 11-12, 23-25, 28, and 32-33 of Application No. 10/310677.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Response to Arguments***

Applicant's assert on page 21, that the claims of the 10/310677 will be amended to remove the non-statutory double patenting rejection or that a terminal disclaimer will be filed. This response has been reviewed. It is noted that the rejection will be maintained until a terminal disclaimer is filed or the claims in application 10/310677 are amended.

***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is (573) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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